

ORIGINAL ARTICLE

Proactive interception and care of Frailty and Multimorbidity in older persons: the experience of the European Innovation Partnership on Active and Healthy Ageing and the response of Parma Local Health Trust and Lab through European Projects

Yari Longobucco¹, Chiara Benedetti¹, Sara Tagliaferri¹, Vincenza Valentina Angileri¹, Elisa Adorni¹, Michele Pessina¹, Luna Zerbinati¹, Lorenzo Cicala¹, Giovanna Pelà¹, Vittoria Giacomini¹, Mirca Barbolini², Fulvio Lauretani^{1,3}, Marcello Giuseppe Maggio^{1,3}

¹Department of Medicine and Surgery, University of Parma, Parma, Italy; ²Public Health and European Commission Senior Expert; ³Medicine-Geriatric-Rehabilitation Department, University-Hospital of Parma, Parma, Italy

Summary. According to the 2018 European Union Ageing Report, the demographic profile of the European population is projected to be older. Aging cannot be considered a homogeneous process, and only in certain cases is “successful”, with maintained functional ability, which is determined by intrinsic capacity, the environment, and their interaction. When intrinsic capacity is lost, elders with chronic diseases develop frailty, a condition with high-risk of disability. Old-age dependency-ratio is projected to increase from 29.6% to 51.2% in the EU in 2070: thus, the need of new approaches targeting the prevention of disability. Numerous studies are conducted in the European Innovation Partnership on Active and Healthy Ageing and addressing identification, treatment, coordination and integration of care in frail older subjects. SUNFRAIL is aimed at developing a model, good practices and tools to improve the identification, prevention and care of frailty and management of multimorbidity. SPRINTT is testing the effectiveness of a multi-component treatment able to treat frailty and sarcopenia. VIGOUR, a project aimed at strengthening integrated-care in different contexts of European Countries, verifies enablers and obstacles encountered in the real world by these good practices. Through the creation of Parma-Lab and Frailty-Team in the Academic-Hospital of Parma combined with the contribution of Parma Health-Trust in the “Community Health-Centers”, the Projects were translated into Health Services Arena. This response bridging European Studies and clinical practice, aims to early detecting and caring 75-year older citizens with frailty and multimorbidity, living in the community, not institutionalized and at risk of hospitalization and mobility ADL-disability. (www.actabiomedica.it)

Key words: ageing, frailty, sarcopenia, multimorbidity, integrated care

Epidemiology of aging in Europe and Italy

According to the 2018 European Union Ageing Report the demographic profile of the European population is projected to change dramatically over the coming decades, with older people accounting for an increasing proportion. The percentage of citizens in

the EU aged over 65 is predicted to rise from 18% to 28% by 2060; the percentage of over-80s will increase from 5% to 12% during the same time-period (European Commission, 2015). The proportion of older people aged 65 and over will become a much larger share, rising from 19% to 29% of the population, while the share of those aged 80 and over will increase from

5% to 13%, becoming almost as large as the young population in 2070. As a result, the demographic old-age dependency ratio (people aged 65 or above relative to those aged 15–64) is projected to increase from 29.6% to 51.2% in the EU as a whole over the projection period (1).

The comparison between 2015 and the estimates of 2080 shows how the European population will continue to age (2). The progressive aging of the elderly population is particularly interesting, with the exponential increase of the cohorts of the over 80s and the doubling of the dependency index of the elderly (that is, the ratio between the elderly population and the working age population [15–64 years]) which will increase from 28.8% in 2015 to 51.0% by 2080 (2). The interval between the overall life expectancy and the healthy life expectancy represent the time during which the living conditions of the population are characterized by higher levels of frailty and disability (3). Furthermore, epidemiological data (ISTAT) referring to Italian population support the European trend showing that aged 65 years or more will increase from 22.3% in 2017 to 33.3% in 2065 (4).

The population progressive ageing trend and the increased demand for health and social care, coupled with countries reduced resources for health and social services, hampers further the access to care for individuals with frailty and multimorbidity conditions, especially in people with lower economic status. It is therefore important to address these conditions taking into consideration overall individual's biomedical and socio-economic factors by considering equity, prevention and sustainability as main key principles.

Heterogeneity of ageing Process: toward healthy ageing and intrinsic capacity

Ageing cannot be considered a homogeneous process, as it includes different potential trajectories. Ageing can be “successful” or healthy, characterized both by the absence of significant chronic diseases, by a level of health perceived as satisfactory, and by the presence of self-sufficiency with satisfactory temporo-spatial orientation. Defining healthy ageing is a prerequisite to promoting it (5). A definition provides a common language that facilitates person-centered care and care

planning. The World Health Organization (WHO) defines health as “complete physical, mental and social well-being, not merely the absence of disease or infirmity” (6). Definition of healthy ageing with multiple implications that recognises the importance of concepts and central to geriatrics, such as culture, function, engagement, resilience, meaning, dignity, and autonomy, in addition to diminishing chronic disease (7).

To address these principles, in 2012, the European Commission has launched the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA), in order to tackle the potential and challenges of ageing in the EU (8).

Specific objective of EIP on AHA is to promote the clinical best practices that combine the biopsychosocial model of function, disability, and health, emphasising abilities and participation of the older adults in their families, work, and communities (9). In addition to disease-based cure, treatment, and comfort, a primary endpoint for healthy ageing is optimising functional status. Then healthy ageing can be defined as “the process of developing and maintaining the functional ability that enables well-being in older age” (10). Functional ability is determined by intrinsic capacity (the composite of all the physical and mental capacities of an individual), the environment, and the interactions between the two (11).

Intrinsic capacity is the composite of all the physical and mental capacities of an individual. Five different domains can be proposed as of primary interest for better defining the intrinsic capacity framework: (i) cognition, (ii) psychological (including mood and sociality), (iii) sensory function (including vision and hearing), (iv) vitality, and (v) locomotion (including muscular and strength function) (12).

In a perspective where aging must be taken into consideration in good health, the concept of resilience is also fundamental because of its ability to capture the adaptation and responsiveness to adverse events.

Traditional models of healthy ageing suggest that having a high level of functioning across a number of domains is a required capacity; resilience is present when a high level of functioning is present after a negative event, or some form of adversity (13). Among the factors that may make the subject more vulnerable there are: genetic predisposition, familial heritage, so-

cio-environmental factors, early life stress, and chronic illness or treatment largely determining vulnerability to psychiatric disorders such as Major Depression or anxiety disorders. Moreover, other factors that make the subject more resistant to stressor attacks are positive emotions socio-environmental factors, cognitive flexibility, and exercise.

Animal studies support the role of an enriched environment for coping different tasks related to stress and depression measures as examples of stressful conditions. The environment concurs to better aging trajectories (14).

Models of Functional decline

Where and when disruption of resilience mechanisms occurs, stressors take precedence over adaptation mechanisms, leading to the development of functional decline reaching in certain cases the loss of self-sufficiency. In these cases, severe reduction in cognitive abilities and the presence of numerous chronic-degenerative diseases, result in mobility impairment and quickly leading to the condition highly associated with elevated risk of institutionalization of the elderly population, the mobility and ADL-disability, where coexistence of both cognitive and physical frailty could contribute to the developing of disability (15). Therefore, the concept of loss of autonomy does not include only the physical domain defined as the ability to carry out an activity in different areas, but also affect psychological (cognitive, emotional and behavioural), and finally social-economic context as the ability to maintain interpersonal relationships within the family and the community (16, 17).

Frailty

Definition and Projects

In the framework of functional decline, halfway between the normal state of functional independence and the pathological one of disability, is the condition of frailty, which affects not only the physical domain, but also the psychological and social one (18).

The term frailty refers to condition of increased vulnerability and poor resolution of homeostasis when

facing a stressor event. This situation, which is dynamic and multidimensional, leads to an increased risk of adverse health outcomes. The occurrence of factors such as acute illnesses, chronic diseases and one's own genetic heritage, have negative impacts on the development of frailty (19, 20). Frailty is correlated to age-related, dynamic, stochastic, non-linear and multidimensional depletion of the systems which leads to a loss of physiological reserve and redundancy in which even minor stress factors can lead to negative outcomes and complications due to the lower capacity of the system to recover homeostasis (21-26).

The consequences of frailty include increased morbidity, risk of falls, social isolation, institutionalization and ultimately mortality and reduced quality of life and independence.

In this way, frailty and multimorbidity defined as the co-occurrence of two or more chronic diseases in the same individual, increase over time together (27).

Frailty is configured as a dynamic process (28) that needs to be readily recognized and treated promptly in order to prevent worsening of functional abilities and the appearance of disability.

In this regard, Figure 1 shows similarities and differences between oncology and geriatric medicine. The new challenge of geriatric medicine is to be identified in the need of capturing symptoms and signs requiring a combined physical and cognitive approach and ranging from "hyperplasia" stage to "cancer development".

Frailty is also frequently associated with sarcopenia, defined as "muscle loss together with a loss of function" as measured by grip strength and muscle mass" and where severity is identified by low physical performance assessed by 4-meter gait speed, Short Physical Performance Battery (SPPB), Timed up and go test (TUG), and 400 meter (29).

Numerous studies are currently conducted on frailty in the European context (Figure 2). The SUN-FRAIL Project, coordinated by Emilia Romagna Region with the scientific support of Parma Health Trust, is aimed at developing and experimenting a model, good practices and tools to improve the identification, prevention and care of frailty and management of multimorbidity, while the Sarcopenia and Physical fRailty IN older people: multi-component Treatment strategies (SPRINTT) is testing the effectiveness of

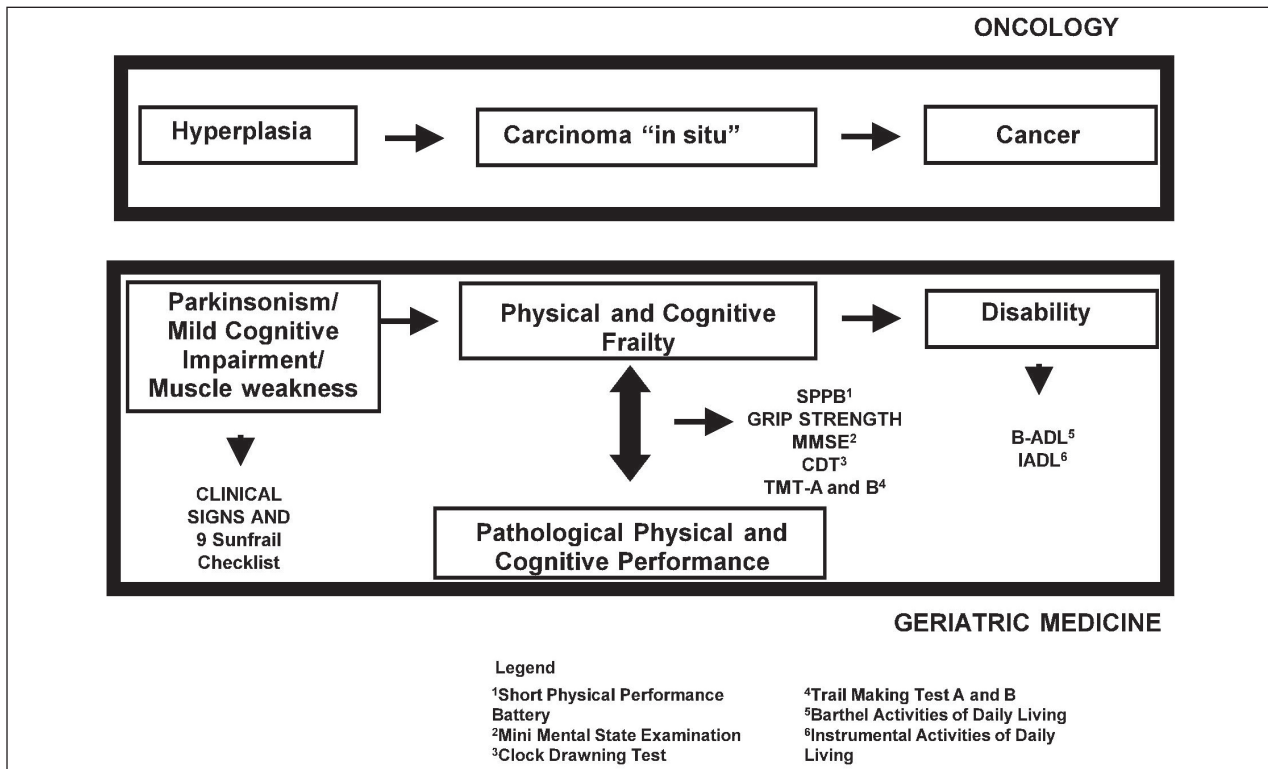


Figure 1. “New era” of the geriatric medicine: standardization of the physical and cognitive frailty in elderly patient: similarities with cancer development in oncology

a multi-component treatment able to treat frailty and sarcopenia (30).

The potential enablers and obstacles encountered in the real world by these promising good practices are presently addressed through the VIGOUR, a European project aimed at strengthening integrated care in different organizational contexts of European Countries.

Screening and Identification of frailty: Sunfrail

There is increasing number of researchers supporting the multidimensional nature of frailty (31). Authors suggest that frailty cannot be limited to physical domain, but necessarily involve psychological, cognitive, emotional, social and spiritual aspects (32). The SUNFRAIL project has the general objective to improve the early identification process of the frail subjects, having as target population the people aged over 65 who live in the community, through initiatives

managed by local health and social services providers in European countries.

By addressing the common aspects and peculiarities of different European health and social care systems and services, the SUNFRAIL project developed common quality standards for the management of frailty and multimorbidity.

Particularly, the Sunfrail Tool is a nine-question, easy to use tool designed to identify frailty risk factors and multimorbidity according to the bio (physical), psycho (cognitive and psychological) and social domains. It can be administered by professionals and community actors, generating an initial “alert” for further investigations or activation of pathways within the health, social and community systems. The Sunfrail Tool was developed by an international multidisciplinary team (composed of geriatricians, sociologists and public health experts) following the methodology indicated for the creation of questionnaires (33-35). The team identified a minimum set of items starting from

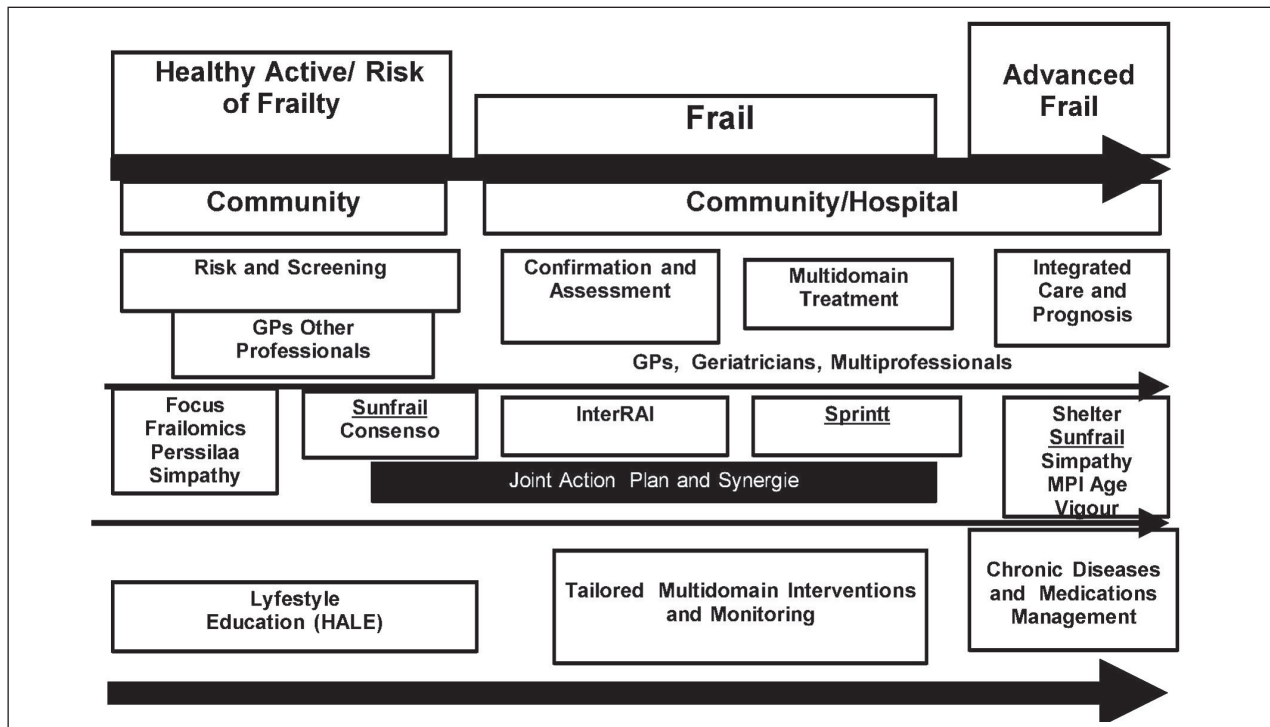


Figure 2. Frailty as continuum from initial assessment to integrated care according to frailty status. In the first line, we describe categories of older individuals, in the second the settings, in the third the European Projects targeting different stage of frailty, and in the bottom line proposed interventions according to different European Projects and Initiatives. Finally, underlined, the Projects described in the Manuscript

already existing tools in the literature, in particular the Edmonton Frailty Scale (36), the Tilburg Frailty Indicator (37) and the Gerontopole Frailty Screening Tool (38); the reference model is the bio-psycho-social model. After a debate, 9 items were selected, 5 of which in the physical domain, 1 in the cognitive domain and 3 in the socio-economic domain. The 9-item Sunfrail Tool, does not produce a numerical score. Based on the alerts generated by the administration of the tool, frailty and related risk factors need to be confirmed through Comprehensive geriatric assessment (CGA) in order to orient care.

The project has also designed the Sunfrail Tool for Human Resources Development; a short, multidisciplinary training program on frailty and multimorbidity according to the bio-psycho-social model. The experimentation of the Sunfrail Tool in various European settings involved 651 older adults over 65 years of age. The main results confirmed the capacity of the Tool to identify frailty and related risks in the population

over 65, especially in primary care and community settings. The Tool appeared particularly suitable to identify frailty risks in a population without clear signs of disability or un-known by services and to orient the selection of preventive care pathways.

An assessment conducted on beneficiaries and professional opinions highlighted that the Sunfrail Tool is understandable, easy to use in every day practice, facilitating access and linking health, social and community services. It proved to be effective in raising older adult awareness on frailty risk factors and on services available, in strengthening professional's knowledge and approach to frailty and facilitating the connections among existent health, social and community services.

The experimentation of the Sunfrail Tool for human resources indicated that an interdisciplinary, intersectoral and multiprofessional approach is essential to promote teamwork, integrated care and coordination among services.

Overall, the Sunfrail project promoted a change of mindset and management approach.

The requests for adoption from professionals (GPs, nurses), local authorities, Italian and European regions, the commitment for further funding, the design of additional pilot studies and the creation of permanent stakeholder groups confirm the achievement of project's expected outcomes.

Assessment and multidomain treatment of physical frailty: SPRINTT

Once the condition of physical frailty is identified (SPPB is one of the most used tests and score ranging from 3 to 9 suggest the presence of frailty), together with its one of the main biological substrates, sarcopenia, various interventions have been proposed to maintain older individuals in good health and active status as long as possible (Figure 3) (39). In particular, through the European SPRINTT project (Sarcopenia and physical frailty in older people: multi-component treatment strategies), a randomized control trial conducted in frail sarcopenic older subjects 70 yr and older, to compare and demonstrate the effectiveness of

a multi-component intervention composed of physical activity, nutritional and technological intervention, versus educational intervention (40). The primary endpoint of the study is to reduce the incidence of motoric-disability, defined as the participant's inability to complete a 400-meter walk in 15 minutes without sitting, without the help of another person or using a walker and without stopping for more than 1 minute at a time.

The secondary endpoints of the study are:

- a) Changes in physical performance parameters
 - SPPB;
 - Dynamometric analysis of the upper limb (handgrip strength);
 - Activities of Daily Living (ADL);
 - Instrumental ADL (IADL);
 - 4 meters walking speed;
 - Pepper Assessment Tool for Disability (PAT-D).
- b) Changes in body composition (measured by DXA), anthropometric parameters (body mass index, circumference of half arm, calf circumference) and nutritional status (Mini Nutritional Assessment-Short Form, MNA-SF).

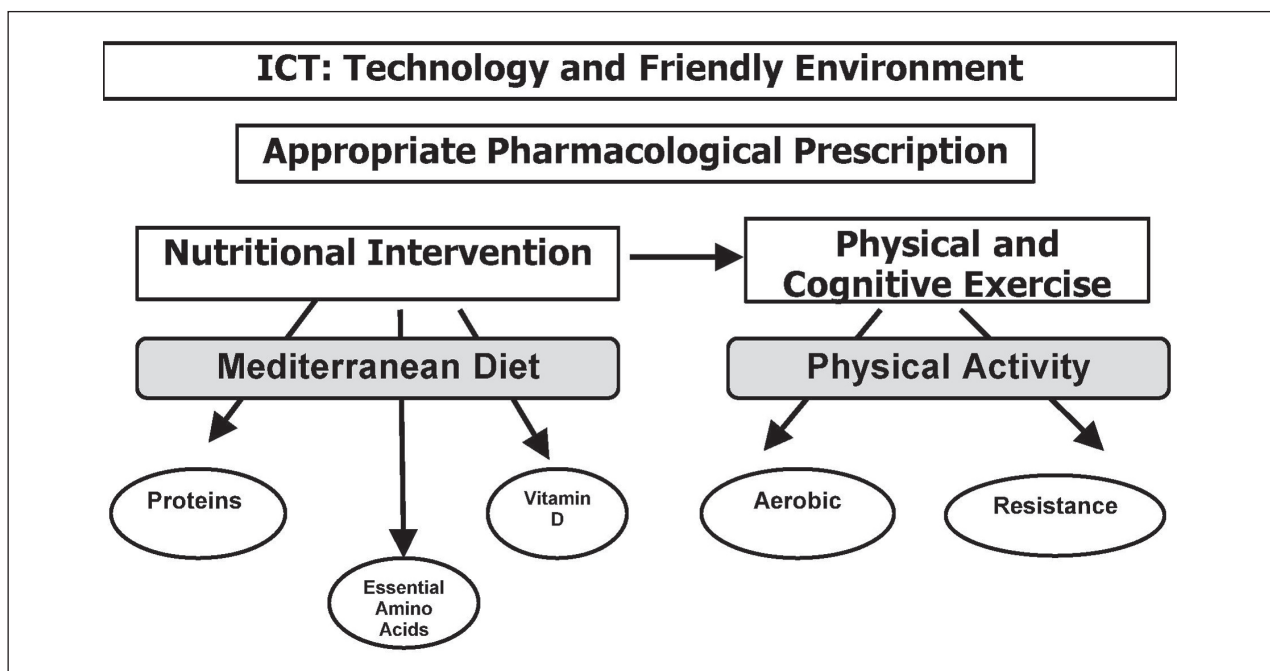


Figure 3. Multiple approach to Physical and Cognitive Frailty

- c) Changes in cognitive function (assessed by MMSE) and mood (via CES-D scale).
- d) Incidence of falls (assessed through questionnaires filled in by the participants and through the use of a dedicated technological device).
- e) Changes in the quality of life (assessed through the EuroQol-5D tool).
- f) Differences in the use of health resources (including day hospital, first aid, hospitalization, use of other care facilities).
- g) Mortality rate.

This five-year project is the result of a rich collaboration between 18 major research institutes in the geriatric field in 11 European countries, including the University of Parma.

SPRINTT project represents the opportunity to agree on a therapeutic indication, the end-points and the clinical trial methodology that will allow developing innovative treatments for this geriatric syndrome that is currently under-diagnosed.

This is the first European clinical trial of an interventional and non-competitive nature, on elderly patients affected by sarcopenia, which will allow the use of physical activity as a reference point for future studies with experimental drugs.

SPRINTT is based on the LIFE study (41, 42), a multicentric randomized controlled trial conducted in the United States, who studied the effectiveness of physical activity in more than 1600 elderly sedentary people at risk of disability. The study showed that a moderate-intensity physical activity program reduces the incidence of major motor disabilities of more than 2.6 years (18). The SPRINTT protocol is oriented to propose on a large scale a protocol of activities to improve the lives of older people.

Other goals of SPRINTT study are to identify the biomarkers of anabolism and muscle catabolism in this population and to develop an economic health model concerning physical frailty and sarcopenia in a real-life context.

In detail, the treatment envisaged in the SPRINTT protocol foresees the division into two groups: the experimental group follows a multi-component intervention (MCI) while the control group follows a program of education lessons to a healthy lifestyle (HALE). A part of the activity carried out in

the MCI concerns physical activity, with walking as the first exercise to prevent or postpone the primary disability outcome, the inability to perform the 400 m walking test; the program of physical activity is completed by exercises of balance, strength and flexibility.

Another section of the protocol comprises nutritional intervention, based on a nutritional counselling, aiming at two main targets:

- a total energy intake of 25-30 kcal/kg of body weight;
- an average daily protein intake of 1.0-1.2 g/kg of body weight.

At last, the treatment includes a technological monitoring, in order to evaluate changes in levels of physical activity.

The Modernization of health care systems: the VIGOUR Project

VIGOUR aims to effectively support health authorities in the process of transformation and modernization of their health and care systems towards integrated and sustainable care models. The project will allow these authorities to customize the design of services aimed at patients with multidimensional needs, using innovative approaches to risk stratification, monitoring and provision of services. It will also support authorities in defining strategies - sensitive to the local context - for integrating good practices and consolidating existing knowledge and tools within integrated assistance.

The Real World of Frailty: the response of Parma Health Trust

Parma Health Trust of Emilia Romagna Region, is responsible for the delivery of primary care, hospital care, outpatient specialist care, public health care, and health care related to social care. The AUSL operates through the districts, at which level local councils and health services determine requirements, plan health and social services, and assess results.

Primary health and social care services are provided through the "Community Health Centers" (Case della Salute), acting as the main pillars for the integrated care through multidimensional evaluation of people with complex health and social care needs,

design and coordinate the integrated care from and to the hospital. Primary and secondary prevention, case detection, management and support to self-management (through telemedicine) are essential components of care delivered with the active participation of patients and voluntary associations.

Emilia Romagna Region Risk Stratification model using longitudinal administrative databases (health and social care), estimates the risk of hospitalization and death for the resident adult population and creates 'patient risk profiles', allowing proactive case management within Primary Health and Social Care services network.

The Azienda Ospedaliero-Universitaria of Parma acts as a secondary care focal point for the integrated care of patients with complex needs, through multi-dimensional evaluation, providing the indications for the individualized care plans (PAI), collaborating to identify the patient's care pathway and to monitor the interventions.

Furthermore, the University Hospital of Parma is a highly specialized polyspecialistic hospital offering a complete range of diagnostic, therapeutic and rehabilitative services. Since 2015 the Geriatric Clinic Unit, in close collaboration with the Emilia-Romagna Region, provides scientific support to the activities of the European Partnership for Innovation on Healthy and Active Aging (EIP-AHA), particularly to the Working Group A3 on Frailty and of the European Reference Sites Network. It also provides scientific support to relevant EU projects and initiatives in the field of functional and cognitive decline in older persons (Sunfrail, the EU Joint Action on Frailty Advantage, SPRINTT and Vigour). Particularly, the Geriatric Clinical Lab of Parma has acquired a unique experience in developing a patient-centered approach to frailty and multimorbidity through the step approach described in the next paragraph.

The Real World of Frailty: the response of Parma Lab and Team of Academic Hospital

The daily activity in the proactive care of frail and sarcopenic older individuals and application /participation at the above-mentioned European Projects allowed the stepwise process with different phases:

1. Setting up of a multiprofessional team composed of two geriatricians, one cardiologist, two young physicians, one nutritionist biologist, two community nurses, one physiotherapist and two motoric scientists.
2. Creation of a lab located in pavilion 27 of the Parma Hospital, where a multidisciplinary team uses equipment such as ultrasound scanners (for chest, abdominal and muscle ultrasound), BIA, GAITRite system and an equipped gym.
3. The activities performed by the Geriatric Clinical Lab of Parma in screening and confirmation of frailty and sarcopenia, in close collaboration with Community Health Centers (Case della Salute), included and are still including:
 - a) Enrollment of subjects in the SPRINTT study; these subjects have a high clinical-assistance complexity requiring the constant presence of a multi-professional team (43).
 - b) Screening of frailty in primary care setting, mainly by nursing staff, using the SUN-FRAIL tool. Potentially frail subjects were invited to perform a 2nd level multidimensional visit (by geriatricians, physicians and nurses). More than 900 subjects in the Parma Health Trust were screened in seven Community Health Centers (Case della Salute), with the participation of associated general practitioners.
 - c) Confirmation of frailty by the Geriatric Clinical Lab of University-Hospital of Parma, two Community Health Centers and a General Practitioner Unit. The tests used were the Mini Mental State Examination and the Short Physical Performance Battery, combined with a pharmacological survey. The frail subjects eligible for the SPRINTT study underwent a complete geriatric visit with a Dual Energy X-Ray Absorptiometry (DEXA), in order to assess the condition of Sarcopenia. The frail and sarcopenic subjects also underwent a complete cardiology visit, to evaluate the safety to perform the physical activity required by the study protocol safely.
 - d) Individualised care plans and proactive responses identified for individuals with mul-

timorbidity, focusing on prevention and tailored care. People with multimorbidity define good health and well-being as enjoyment of life, maintenance of independence, having social relationships and participating in society (43). The study of multimorbidity does not disregard the study of the subject's function. This complete evaluation allows the application of various targeted treatments based on the complexity of the subject, its functional reserve, its nutritional status and polypharmacy. Regarding the treatment, the nutritional intervention is managed by the nutritionist biologist, while physical activity is administered by the physiotherapist or by motoric scientists according to the participant's needs, with the clinical supervision of a physician and a nurse. Each patient condition and performance is then monitored and discussed in the framework of a staff meeting in which the various possible multicomponent interventions can be taken into consideration. The staff meets twice a week and promotes health with a multi-domain approach.

- e) Overall, educational activities on the concept of healthy and active ageing are performed in order to increase local awareness on this topic in the oldest population. The campaign was realized from October 2016 to November 2017 for the specific goal of SPRINTT recruitment and is still ongoing through the collaboration and support of various stakeholders including patients and citizen organizations (University of the Third Age and AUSER), Municipalities, and trade unions (Coldiretti and CUPLA).

Furthermore, through the newly funded VIGOUR project, integrated care will be enhanced by strengthening professional and functional integration among the available primary care and hospital services network, in order to avoid inappropriate hospitalization and to facilitate hospital discharge. Emilia Romagna Region plans to participate by working on identifying frailty and multimorbidity in older persons over 75 (especially in community-primary care set-

tings), through the combined application of the Risk stratification and the Sunfrail tool.

Conclusions

If successful, the approach described and the translation of these European Projects into Health Services arena, could provide a suitable response, in terms of organization and strategies, to frailty and multimorbidity in 75 year older citizens living in the community, not institutionalized and at potential risk of hospitalization and mobility and ADL-disability. All these timely interventions could slow down and reverse the functional decline in these subjects. Not less, the involvement of the stakeholders including patients and citizen organization can represent a response to the social needs of this particular population. In this way, the aging process can be reported on the tracks of healthy and active aging according to all aspects of the biopsychosocial model.

Acknowledgements

We thank Sprintt participants and their families, Maurizio Conca, Pasquale Rosanova, Maria Teresa Zanelli, Franco Ferrari, and Pietro Schianchi from Department of Medicine and Surgery of University of Parma, University-Hospital of Parma, AUSER Parma and Coldiretti Senior for their enthusiastic support.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Eurostat. Population by age group. By Eurostat Data 2017. <http://ec.europa.eu/eurostat/tgm/refreshTableAction.do?tab=table&plugin=1&pcode=tps00010&language=en>
2. Eurostat. Population structure and ageing. Eurostat yearbook. Statistics explained.2017.http://ec.europa.eu/eurostat/statisticsexplained/index.php/Population_structure_and_ageing.
3. Beltrán-Sánchez H, Soneji S, Crimmins EM. Past, Present, and Future of Healthy Life Expectancy. *Cold Spring Harb Perspect Med* 2015 Nov 2; 5(11). pii: a025957.
4. Istat. Il futuro demografico del paese. By Istat Data 2018. https://www.istat.it/it/files/2018/05/previsioni_demografiche.pdf

5. Benziger CP, Roth GA, Moran AE. The Global Burden of Disease Study and the Preventable Burden of NCD. *Glob Heart* 2016; 11: 393-7.
6. Grad FP. The preamble of the constitution of the World Health Organization. *Bull World Health Organ* 2002; 80: 981-984.
7. Phelan EA, Anderson LA, LaCroix AZ et al. Older adults' views of "successful aging"—how do they compare with researchers' definitions? *J Am Geriatr Soc* 2004; 52: 211-216.
8. Bousquet J, Michel J, Standberg T, Crooks G, Iakovidis I, Gomez M. The European Innovation Partnership on Active and Healthy Ageing: the European Geriatric Medicine introduces the EIP on AHA Column. *Eur Geriatr Med* 2014; 5: 361-2.
9. Friedman SM, Mulhausen P, Cleveland ML, et al. Healthy Aging: American Geriatrics Society White Paper Executive Summary. *J Am Geriatr Soc* 2019 Jan; 67(1): 17-20.
10. Beard JR, Officer A, de Carvalho IA, et al. The World report on ageing and health: a policy framework for healthy ageing. *Lancet* 2016; 387: 2145-2154.
11. Beard JR, Bloom DE. Towards a comprehensive public health response to population ageing. *Lancet* 2015; 385: 658-661.
12. Cesari M, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, et al. Evidence for the Domains Supporting the Construct of Intrinsic Capacity. *J Gerontol A Biol Sci Med Sci* 2018 Nov 10; 73(12): 1653-1660.
13. Cosco TD, Howse K, Brayne C. Healthy ageing, resilience and wellbeing. *Epidemiol Psychiatr Sci* 2017 Dec; 26(6): 579-583.
14. Sampedro-Piquero P, Alvarez-Suarez P, Begega A. Coping with Stress During Aging: The Importance of a Resilient Brain. *Curr Neuropharmacol* 2018 Mar 5; 16(3): 284-296.
15. Lauretani F, Meschi T, Ticinesi A, Maggio M. "Brain-muscle loop" in the fragility of older persons: from pathophysiology to new organizing models. *Aging Clin Exp Res* 2017 Dec; 29(6): 1305-1311.
16. Stuck AE, Walthert JM, Nicolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med* 1999; 48: 445-69.
17. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci* 2000; 55(4): M221-31
18. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 2006; 54(6): 991-1001
19. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K, Frailty in elderly people. *Lancet* 2013; 752-762.
20. Xue QL, The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011; 1-15.
21. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A: Biol Sci Med Sci* 2001; M146-M157.
22. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people, *Can Med Assoc J* 2005; 489-495.
23. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; 24.
24. Rockwood K, Mitnitski A. How might deficit accumulation give rise to frailty? *J Frailty Aging* 1 2012; 8-12.
25. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011; 17-26.
26. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multi-system physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A: Biol Sci Med Sci* 2009; 1049-1057.
27. Villacampa-Fernández P, Navarro-Pardo E, Tarín JJ, Cano A. Frailty and multimorbidity: Two related yet different concepts. *Maturitas* 2016; 10:008.
28. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. *Gerontology* 2009; 55(5): 539-49.
29. Morley JE. Frailty and Sarcopenia: The New Geriatric Giants. *Rev invest clin* 2016; 68(2): 59-67.
30. Landi F, Cesari M, Calvani R, et al. The "Sarcopenia and Physical Frailty IN older people: multi-component Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. *Aging Clin Exp Res* 2017 Feb; 29(1): 89-100.
31. Gobbens RJ, Luijkx, KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. *Nursing Outlook* 2010; 58: 76-86.
32. Cesari, M, Pahor M, Lauretani F, et al. Frailty syndrome and skeletal muscle: result from Invecchiare in Chianti study. *Am J Clin Nutr* 2006 May; 83(5): 1142-8.
33. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care* 2003; 15(3): 261-6.
34. Burns KE, Duffett M, Kho ME, et al. A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ* 2008; 179(3): 245-52.
35. Bennett C, Khangura S, Brehaut JC, et al. Reporting guidelines for survey research: an analysis of published guidance and reporting practices. *PLoS Med* 2010; 8(8): e1001069.
36. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. *Age Ageing* 2006; 35(5): 526-9.
37. Gobbens RJ, Van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc* 2010; 11(5): 344-55.
38. Tavassoli N, Guyonnet S, Abellan Van Kan G, et al; Geriatric Frailty Clinic (G.F.C.) for Assessment of Frailty and Prevention of Disability Team. Description of 1,108 older patients referred by their physician to the "Geriatric Frailty

- Clinic (G.F.C.) for Assessment of Frailty and Prevention of Disability” at the gerontopole. *J Nutr Health Aging* 2014; 18(5): 457-64.
39. Lauretani F, Ticinesi A, Gionti L, et al. Short-Physical Performance Battery (SPPB) score is associated with falls in older outpatients. *Aging Clin Exp Res* 2018 Dec 4.
40. Cesari M, Landi F, Calvani R, et al. Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial. *Aging Clin Exp Res* 2017 Feb; 29(1): 81-88.
41. Fielding RA, Rejeski WJ, Blair S et al. The Lifestyle Interventions and Independence for Elders Study: Design and Methods. *J Gerontol A Biol Sci Med Sci* 2011; 66(11): 1226-1237.
42. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults: The LIFE Study Randomized Clinical Trial. *JAMA* 2014; 311(23): 2387-2396.
43. Marzetti E, Cesari M, Calvani R, et al. The “Sarcopenia and Physical frailty IN older people: multi-component Treatment strategies” (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants. *Exp Gerontol* 2018 Nov; 113: 48-57.

Received: 2 May 2019

Accepted: 16 May 2019

Correspondence:

Yari Longobucco

Department of Medicine and Surgery

University of Parma, Parma, Italy

Tel. +39 0521 906425

E-mail: yari.longobucco@unipr.it